REMARKS

In the Office Action mailed August 26, 2005, the Examiner rejected claim 72 under U.S.C. § 112, second paragraph, for indefiniteness and claims 10-15, 25, 27, 32-34, 66-68, and 70 under U.S.C. § 112, first paragraph, for lack of enablement. The specific grounds for objection and Applicants' response thereto are set out in detail below.

I. Rejection under 35 USC § 112, second paragraph

The Examiner rejects claim 72 for the recitation of the phrase "sequence comprises consisting of." Applicants have amended claim 72 to remove the term "comprising" thereby clarifying the claim language Accordingly, withdrawal of the § 112, second paragraph, rejection is requested.

II. Rejection under 35 USC § 112, first paragraph

The Examiner has rejected claims 10-15, 25, 27, 32-34, 66-68 and 70 for allegedly lacking enablement. The Examiner has not similarly rejected claim 72.

The Examiner's position appears to be that the field of the invention is unpredictable and the *in vitro* data in the specification are not predictive of *in vivo* success for the number of variants covered by the claims. The Examiner provides various references teaching various things that are intended to detract from the credibility of applicants' invention. Applicants respectfully disagree as a matter of law and fact.

A. The Law

35 USC § 112, first paragraph, mandates that the specification must teach how to make and use the claimed invention. The purpose of this requirement is to ensure that the invention is communicated to the interested public in a meaningful way. *MPEP* Section 2164. The test for determining whether a particular claim is supported by the specification is whether based upon what is in the specification, one of skill in the art of the invention could make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed . Cir. 1988). The fact that experimentation

may be complex does not necessarily make it "undue," if the art typically engages in such experimentation. *In re Wands*, 858 F.2d at 737, 837 USPQ2d at 1404. The factors to consider in determining whether the amount of experimentation required is "undue" are (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Each of these factors are important.

With regard to (G), the working examples *in vitro* data should correlate with *in vivo* methods. As a matter of law, the issue of "correlation" is dependent upon the prior art. If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. But even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F. 3d 1560, 1566, 34 USPQ 2d 1436, 1441 (Fed. Cir. 1995).

With regard to (E), predictability, the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833,839 166 USPQ 18, 24 (CCPA 1970) .

B. The Facts

All of the above "Wands" factors are important in assessing the adequacy of a specification for enablement purposes. However, in the present case, the Examiner focuses on two main things: (1) the predictability in the art; and (2) the working examples, particularly the examples presenting *in vitro* data.

As a threshold matter, Applicants point out that the present claims are not directed to a use or method. Rather, the claims are directed to particular peptides and immunogens and pharmaceuticals comprising the same. The claims recite that such mutant peptides elicit a specific human CD8+ cytotoxic T lymphocyte immune response. Applicants also point out that the specifically claimed peptides have a structure that provides a clear and specific reference point. Applicants are not claiming

any and all peptides that have a particular function. Applicants' claims recite a specific amino acid sequence and designate where specific substitutions may be made and provide the universe of amino acids from which the substituting amino acids can be selected. The claims recite a specific function, *i.e.* to elicit a specific human CD8+ cytotoxic T lymphocyte immune response, so as to further limit the universe of peptides encompassed by the claims. These comments are intended to address the breadth of the claims and provide a framework for addressing the Examiner's concerns.

The Examiner is skeptical that the claimed peptides could function as recited for the alleged reason that the art is unpredictable. She cites Paul (1993) and Apostolopoulos (1998) to support her conclusion. Without challenging what these two references teach, applicants submit herewith a different reference, Carbone DP, Ciernik IF, Kelley MJ *et al.*, "Immunization with mutant p53- and K-ras-derived peptides in cancer patients: immune response and clinical outcome" *J. Clin. Onco.* 23:5099-107 (2005). Carbone reports that a strong correlation between CTL induction *in vitro* and clinical response *in vivo* can be demonstrated using a mutant *ras* peptide-based vaccine regimen. Thus, these data strongly support the idea that mutated *ras* peptides can induce anti-cancer reactivity *in vivo,* likely through CTL induction, and that epitope expression is sufficient on tumors for immune recognition. Furthermore, the observations that both CTL activity and clinical responses were demonstrable indicate that *ras* peptide-based immunotherapy was effective in overcoming potential tumor escape mechanisms. Applicants acknowledge that Carbone is a 2005 reference. However, it does weigh in favor of the operability of the present invention. The potential drawbacks highlighted by the Examiner have not interfered with the operability of analogous inventions.

Arguably, tumor cell "escape host defense mechanisms" would be a concern in all cancer immunotherapies. It is not a phenomenon limited to the presently claimed invention. For instance, if the art accepted the Examiner's argument as reflecting prevailing thought, then all cancer immunotherapies, whether they are based on other kinds of experimental vaccines (*See* Berzofsky JA, Terabe M, Oh S *et al."* Progress on new vaccine strategies for the immunotherapy and prevention of cancer." *J. Clin. Invest.* 113*:* 1515-25 (2004); Gilboa E., "The promise of cancer vaccines." *Nat. Rev. Cancer*;

4: 401-11 (2004); Emens, LA, Jaffee EM. "Leveraging the activity of tumor vaccines with cytotoxic chemotherapy." *Cancer Res.* 65: 8059-64 (2005)) or cell transfer approaches (*See* Dudley ME, Rosenberg SA. "Adoptive-cell-transfer therapy for the treatment of patients with cancer." *Nat. Rev. Cancer* 3: 666-75 (2003)) would be discounted as unbelievable. Yet, this is not the case. All experimental immunotherapies are confronted with the same types of tumor countermeasures as the Examiner discusses in connection with the claimed invention yet cancer immunotherapy is a robust field of research and endeavor. Even current patented oncologic therapies, including anti-neoplastic agents (*See* Dean M, Fojo T, Bates S., "Tumour stem cells and drug resistance" *Nat. Rev. Cancer* 5: 275-84 (2005)) and biologics (*See* Nagata Y, Lan KH, Zhou X *et al.* "PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients" *Cancer Cell,* 6: 117-27 (2004)), face their own limitations because of the complexity of the cancer microenvironment, such as rapid tumor growth rate, antigenic heterogeneity, altered signaling pathways, and stem-cell resistance. Yet, these interventions can work in patient subpopulations, despite a plethora of concerns and/or speculation of why they should fail.

Even if one were to accept the Examiner's argument that tumor escape mechanisms are physiologically relevant to the present invention, studies by Rosenberg and colleagues (Dudley ME, Rosenberg SA. "Adoptive-cell-transfer therapy for the treatment of patients with cancer", *Nat. Rev. Cancer* 2003;3:666-75, (2003); Dudley ME, Wunderlich JR, Robbins PF *et al.* "Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes" *Science*, 298:850-4 (2002)) in the area of adoptive cellular immunotherapy clearly shows that an antitumor T lymphocyte response can causally eradicate even advanced bulky or metastatic disease. Presumably, if such tumor escape mechanisms are operative in those patients, then one must conclude that the immune response is an adaptive and powerful biologic weapon that can overcome a potential gamut of tumor countermeasures, including those cited here.

The Examiner also raises the issue of antigen loss variants. However, applicants believe this is less of a concern in the case of tumor cells that express

mutated *ras* genes. Applicants believe this to be true because the mutated *ras* gene(s) is crucial for the maintenance of the transformed state (*See* Bos JL. "*ras* oncogenes in human cancer: a review" Cancer Res. 49:4682-89 (1989); Abrams SI, Hand PH, Tsang KY, Schlom J. "Mutant *ras* epitopes as targets for cancer vaccines. Semin." *Oncol.* 1996; 23:118-34 (1996)). If tumor cells lose expression of this oncogene, which incidentally encodes the T cell epitope(s), then neoplastic tissue will lose malignant potential. Thus, as long as a cancer that harbors a mutated *ras* gene is evident, then the mutated gene and its corresponding epitope(s) will also be expressed. Additionally, the issue of tolerance or deletion becomes less of concern here because mutated *ras* genes encode non-self antigens (*See* Abrams SI, Hand PH, Tsang KY, Schlom J. "Mutant *ras* epitopes as targets for cancer vaccines." *Semin. Oncol.* 1996;23:118-34 (1996)).

Thus, CTL precursors in patients are likely to exist. The cited study by Fossum *et al.* (Fossum B, Gedde-Dahl I, T. , Breivik J *et al.* "p21-*ras*-peptide-specific T-cell responses in a patient with colorectal cancer. CD4+ and CD8+ T cells recognize a peptide corresponding to a common mutation (13Gly-->Asp)" *Int. J. Cancer* 56: 40-5 (1994)) regarding antigen loss could be the result of incomplete analysis of the tumor sample, as well as a number of other technical or scientific reasons. It remains unproven, however, that the absence of the *ras* mutation in the tumor sample of that patient was a direct consequence of antigen loss and tumor escape. In fact, Applicants assert that antigens encoded by mutated *ras* genes are likely to be more stably expressed because *ras* oncogenesis in this classification of neoplastic diseases is essential for maintenance of the malignant state. Moreover, a recent study by Linard *et al.* (Linard B, Bezieau S, Benlalam H *et al.* "A ras-mutated peptide targeted by CTL infiltrating a human melanoma lesion" *J. Immunol.* 168: 4802-8.13 (2002)) provides direct evidence that tumor cells harbored and/or retained expression of the relevant *ras* peptide *in vivo*.

The point of the above discussion is two-fold. First, not all of the Examiner's concerns are valid. There have been successes in analogous technologies despite the same alleged drawbacks. Second, the amount of experimentation needed to practice the presently invention is not undue. The amount of experiment needed is routine for

this field. This is true even as the claims are presently drafted. The issues the Examiner raise pertain to any *ras* peptide variant. It doesn't matter that a multitude of different variants are encompassed by the claims. The issues remain the same regardless of the precise amino acid sequence of a given peptide and regardless of the type of cancer immunotherapy at issue. The point is that those issues are addressed as a matter of routine in the field of the invention and in analogous technologies. As such, the operability of the claimed invention would be believable to the skilled artisan.

The Examiner also takes issue with the *in vitro* data in the specification. In response, applicants assert that CTL activity *in vitro* has been widely accepted in the immunotherapy field as a useful surrogate bioassay for "proof-of-principle" and potential efficacy (Hobeika AC, Clay TM, Mosca PJ, Lyerly HK, Morse MA. "Quantitating therapeutically relevant T-cell responses to cancer vaccines". *Crit. Rev. Immunol* 21:287-97 (2001)). Moreover, in the recent study using a mutant *ras* peptide-based vaccine regimen, Carbone *et al., supra*, demonstrated a strong correlation between CTL induction *in vitro* and clinical response *in vivo*, as noted above. Thus, these data support the idea that mutated *ras* peptides can induce anti-cancer reactivity *in vivo* likely through CTL induction, and that epitope expression is sufficient on autochthonous tumor for immune recognition.

Applicants assert that the present claims meet the legal requirement for enablement because based upon what is in the specification, one of skill in the art of the invention could make and use the invention without undue experimentation. Although the Examiner correctly recognizes that the field of the invention is complex and that a certain amount of experimentation is required, such experimentation is not undue for the field of the invention. The obstacles highlighted by the Examiner are obstacles to the field of cancer immunotherapy, in general. The breadth of the present claims does not have any bearing on the issues the Examiner has raised. Some of the Examiner's concerns are not technically valid or have been shown to not be relevant. Other issues may be legitimate concerns but have not been obstacles to success in analogous technologies. Applicants have shown that the *in vitro* data presented in the specification is accepted as being predictive of success *in vivo* in the field of the invention. In view of Applicants' comments as supported by the attached references,

Applicants respectfully request the Examiner to reconsider and withdraw the rejection for lack of enablement.

CONCLUSION

Applicants respectfully request the Examiner to enter the above amendment. In view of the above remarks and amendments, Applicants respectfully submit that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

If any additional fees are required for the filing of this paper, Applicants authorize the Commissioner to charge any deficiency to Deposit Account No. 08-1641.

Respectfully submitted,

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